PE3/18

Long-term safety and efficacy of rilpivirine in combination with nucleoside/ nucleotide reverse transcriptase inhibitors in HIV-1 infected patients: 7-year roll-over study of phase 2 and 3 clinical studies

Jean Michel Molina[1*], Gerd Fätkenheuer[2], Eric Van Wijngaerden[3], Pedro Cahn[4], Luminita Ene[5], Johan Lombaard[6], Natalia Zakharova[7]; Veerle Van Eygen[8]; Simon Vanveggel[8]; Rodica Van Solingen-Ristea[8]

[1]University of Paris Diderot, Hôpital Saint-Louis, Paris, France; [2]Department of Internal Medicine, University of Cologne, KerpenerStraße 62, 50937, Cologne, Germany; [3]Department of general internal medicine, University Hospitals Leuven, Leuven, Belgium; [4]Fundacion Huesped, Buenos Aires, Argentina; [5]Spitalul de Boli Infectioase si Tropicale "Dr. Victor Babes" Bucuresti, Sos. Mihai Bravu nr. 281, Sector 3, Bucuresti, Romania; [6]Josha Research, Box 3530, Bloemfontein, 9300, South Africa; [7]Centre for Prophylaxis and Control of AIDS and Infectious Diseases, St. Petersburg, Russia; [8]Janssen Research & Development, Turnhoutseweg 30, 2340 Beerse, Belgium

*Presenting Author

INTRODUCTION

- Rilpivirine (RPV), a next generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against both wild type and NNRTI-resistant HIV type 1 (HIV-1), was approved in the US in 2011 as single drug and in subsequent years in fixed-dose combinations with other antiretroviral agents for the treatment of adult patients with HIV-1 infection.[1]
- Life-long HIV treatment with simplified dosing regimens, improved safety and tolerability profile and with low rates of resistance development is desired.
- Long-term safety, tolerability and efficacy of RPV in combination with a background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are presented.

OBJECTIVES

- The primary objective of this 7-year roll-over study was to provide continued access to RPV for patients, who had clinical benefit from RPV treatment in phase 2b or phase 3 studies.
- Secondary objectives were to evaluate the long-term safety and tolerability of RPV 25 mg QD in combination with two NRTIs.

METHODS

Study overview

- This phase 3, open-label, multicenter, roll-over study (NCT01266902) included HIV-1 infected patients who were randomized and treated with RPV in the phase 2b (C204, NCT00110305)[2] or phase 3 (ECHO, C209, NCT00540449 and THRIVE, C215, NCT00543725)[3,4] studies.
- All patients continued to receive RPV 25 mg QD in combination with an investigator selected background regimen of 2 NRTIs until RPV became commercially available in the participant's country or were switched to another treatment option per investigator's decision or were withdrawn.

Patients

- Initially antiretroviral treatment-naïve adults (≥18 years) with HIV-1 infection who were treated with RPV in the phase 2b or phase 3 studies.
- At the time of roll-over, in the opinion of the investigator, expected to continue experiencing clinical benefit from RPV treatment.

Study evaluations

Safety

- Adverse events (AE) leading to discontinuation, serious AEs (SAEs), AEs considered at least possibly related to RPV, pregnancies, any grade 3/4 events of rash (irrespective of causality), and HIV-related AEs.
- AEs of special interest (neuropsychiatric events, hepatic events, skin, endocrinology events, and potential QT prolongation-related events).

Efficacy

- Viral load (HIV-1 ribonucleic acid [RNA] copies/mL) and CD4+ cell count measured every 24 weeks.
- Time to virologic rebound, defined as HIV-1 RNA ≥50 copies/mL (confirmed, or single value at last study visit).
- Time to treatment failure, defined as virologic rebound or discontinuation due to any reason except switching to commercially available RPV.
- Absolute CD4+ cell count and change in CD4+ from baseline.

Genotypic analyses

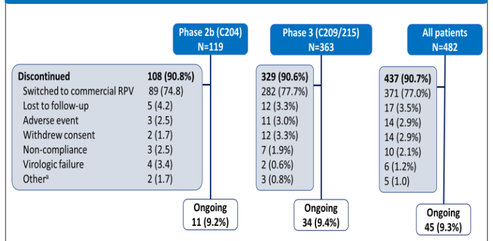
- Genotypic resistance data were collected as per local practice in patients with virologic failure.

RESULTS

Patient disposition and baseline characteristics

- A total of 482 patients were treated: 119 rolled-over from the phase 2b study and 363 from the phase 3 studies.
- 437 (>90%) patients had discontinued the study and 45 (9.3%) patients were ongoing.

Figure 1: Patient disposition



[a]Other reasons for discontinuation include: investigator's decision (n=2), Patient wishes to fall pregnant (n=1), patient switched to darunavir (n=1), patient was imprisoned (n=1)

Table 1: Patient demographics (intent- to-treat population)

Characteristics	Phase2b (C204) (N=119)	Phase 3 (C209/C215) (N=363)	All patients (N=482)
Age (years), median (range)	40.0 (28; 66)	39.0 (22; 69)	40.0 (22; 69)
Men, n (%)	78 (65.5)	279 (76.9)	357 (74.1)
Age category, n (%)			
<50 years	101 (84.9)	311 (85.7)	412 (85.5)
≥50	18 (15.1)	52 (14.3)	70 (14.5)
Race/ethnicity			
White	50 (42.0)	273 (65.3)	287 (59.5)
Asian	43 (36.1)	58 (16.0)	101 (21.0)
Black or African American	17 (14.3)	64 (17.6)	81 (16.8)
American Indian/Alaska Native	0	4 (1.1)	4 (0.8)
Other	9 (7.6)	0	9 (1.9)

The ITT population included all patients who received ≥1 dose of RPV in the study, regardless of their compliance with the protocol and adherence to the dosing regimen; ITT, intent-to-treat; n: number of patients

- Median age at baseline (at the time of roll-over) was 40.0 (range: 22-69) years.
- A total of 1374.8 patient-years of RPV exposure was reported in this study, with a mean (SD) exposure duration of 2.85 (2.4) years.
- History of Hepatitis B or C infection was rare (6%), and none had both co-infections.
- Most frequent HIV-1 subtype was B (57.4%).
- Most of the patients had baseline HIV-1 RNA <50 copies/mL at the time of rollover
- Median CD4+ count at baseline (at time of roll-over) was 563.0 with range (152.0 - 1680).

Safety outcomes

Table 2: Summary of adverse events

n (%)	Phase 2b (C204) (N=119)	Rilpivirine Phase 3 (C209/C215) (N=363)	All patients (N=482)
Patients with at least 1 AE	32 (26.9)	70 (19.3)	102 (21.2)
SAE	9 (7.6)	14 (3.9)	23 (4.8)
Fatal AE	0	2 (0.6)	2 (0.4)
Worst grade 1 or 2 AE	28 (23.5)	59 (16.3)	87 (18.0)
Worst grade 3 or 4 AE	8 (6.7)	9 (2.5)	17 (3.5)
Worst grade 4 AE	2 (1.7)	3 (0.8)	5 (1.0)
AEs leading to discontinuation of study Drug[a]	1 (0.8)	11 (3.0)	12 (2.5)
AE possibly related to study drug	7 (5.9)	16 (4.4)	23 (4.8)
SAE possibly related to study drug	0	1 (0.3)	1 (0.2)
Grade 3 or 4 AEs possibly related to study drug	1 (0.8)	2 (0.6)	3 (0.6)
Patients with ≥1 HIV-related AE	3 (2.5)	7 (1.9)	10 (2.1)

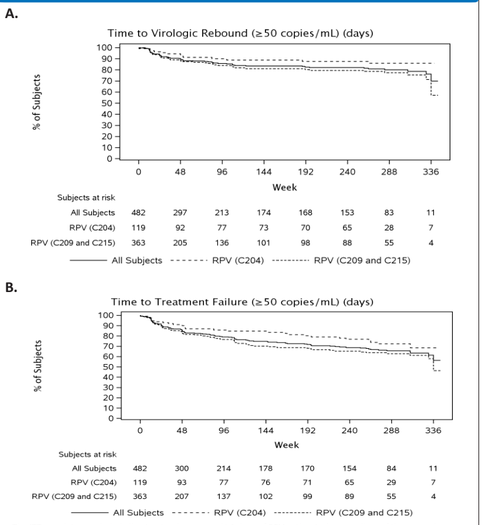
[a]7 patients discontinued study treatment due to pregnancy; AE, adverse events; SAE, serious adverse events

- Adverse events were reported in 102 (21.2%) patients.
- Grade 3 or 4 AEs were reported in 17/482 (3.5%) patients, of which 5 patients had grade 4 AEs.
- SAEs were reported in 23 (4.8%) patients, none were considered by the investigator to be at least possibly related to RPV.
- Two (0.4%) deaths were reported during the study: 1 patient died of gastric cancer and 1 patient died due to unknown reasons.
- Most frequently reported AEs were pregnancy in 7 (1.5%), and syphilis in 5 (1.0%) patients. All who became pregnant discontinued study drug.
- AEs of special interest were reported in 39 (8.1%) patients; the most frequently reported were neuropsychiatric events (14 [2.9%]), AEs leading to discontinuation (12 [12.5%]), and hepatic events (9 [1.9%]).
- Twenty-three (4.8%) patients had AEs at least possibly related to rilpivirine including increase blood serum components in 6 (1.2%) patients (triglyceride, cholesterol, creatinine), skin and subcutaneous tissue disorders in 5 (1.0%), metabolism and nutrition disorders in 4 (0.8%) patients.
- HIV-related AEs were reported in 10 (2.1%) patients.
- There were no grade 3 or 4 events of rash and no QT interval prolongation events.

Efficacy outcomes

Time to virologic rebound/ treatment failure

Figure 2: Kaplan-Meier estimates of time to virologic rebound (A) and treatment failure (B) from baseline using a cut-off of ≥50 copies/mL (ITT population)



The ITT population included all patients who received ≥1 dose of RPV in the study, regardless of their compliance with the protocol and adherence to the dosing regimen; ITT, intent-to-treat

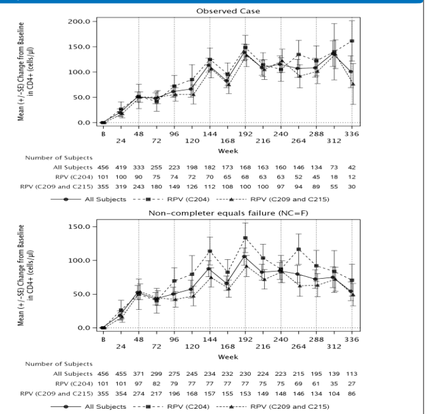
- Through 288 weeks of treatment 80% (95% CI:74.9%; 84.3%) of patients maintained virologic suppression of <50 copies/mL; data is available up to Week 336 (7 of 48-week intervals), but too limited for making conclusions.
- Averaged over the total treatment duration, the rebound rate was 5.5 (95% CI:4.4; 6.9) events per 100 patient years, corresponding to 68/482 (14.1%) of patients having a virologic rebound, 39 of whom had a virologic rebound during the first 24 weeks after roll-over.
- Only 6/482 (1.2%) patients discontinued the study because they reached a virologic endpoint.
- At 288 weeks, Kaplan-Meier estimate for treatment failure was 65.7% (95% CI: 59.8%, 70.9%).

Genotypic analyses

- Post-baseline genotypic data were available for 4/68 patients with virologic rebound (HIV-1 RNA ≥50 copies/mL)
  - RPV resistance-associated mutations (RAM) were observed in 3 patients: Y181C (n=1), E138K + M230L (n=1), and Y181C + E138K + M230L (n=1)
  - Two of these patients with RPV RAMs also had the NRTI RAM M184V

Immunologic Analysis

Figure 3: Mean (SE) change from baseline in CD4+ cell counts over time (ITT population)



The ITT population included all patients who received ≥1 dose of RPV in the study, regardless of their compliance with the protocol and adherence to the dosing regimen; Changes in CD4+ cell count were based on observed case; non-completer = failure (NC=F) approach was used to impute with baseline values (change of 0) in case of discontinuation for reasons other than commercial availability of RPV and LOCF was used to impute intermediate missing values; ITT, intent-to-treat; LOCF, last observation carried forward

- The mean change in absolute CD4+ cell count from baseline increased over time until Week 192. A gradual decrease in the mean change from baseline was observed thereafter based on the NC=F approach, but the mean change from baseline remained fairly constant based on the observed case approach.

CONCLUSIONS

- Long-term treatment with once-daily RPV in combination with two NRTIs was well-tolerated without new safety findings.
- First-line treatment with RPV and 2 NRTIs showed overall good efficacy with the majority of patients (80%) maintaining sustained virologic suppression (i.e., without virologic rebound) through 288 weeks of treatment using a cut-off of ≥50 viral RNA copies/mL.

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